Encephalitis in the immunocompromised host

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Viral encephalitis in the immunocompromised

- **Human Herpesviruses**
  - HSV1, HSV2, VZV, EBV, CMV, HHV6, HHV7, HHV8

- **Polyomaviruses**
  - JC Virus

- **Enteroviruses**

- **HIV**

- **Transplantation (Zoonotic)**
Risk factors

Impaired cell mediated immunity (CMI)
- HIV/AIDS
- Lymphoreticular malignancies (e.g., Hodgkin’s lymphoma)
- Chemotherapy (e.g., Purine analogues-fludarabine)
- Transplantation (Solid, Stem Cell)
- Chronic corticosteroid use (e.g., collagen vascular disease, vasculitis, Chronic renal failure, rheumatoid arthritis)
- Hereditary (e.g., SCID)

Primary infection/re-infection
- Person-Person
- Tissue transplant (solid, stem cell)
- Blood products
- Other

Reactivation latent infection
Encephalitis in the immunocompromised

- Primary infection severe
- Reactivation latent infection \( \Rightarrow \) CNS Dx
- Single or multiple pathogens (simultaneous, sequential)
- Atypical clinical presentation
- Atypical clinical course
- Treatment refractory (resistance)
- Unusual pathogenesis
- Differential diagnoses wide (infectious, non infectious)
Clinical history

- Immune impairment: depth, duration, quality
- Exposures
- Latency
- Antiviral (and other) prophylaxis
- Differentials
  - Postinfectious
    - Acute Disseminated Encephalomyelitis (ADEM)
  - Encephalopathy
    - Reyes, drugs, toxins, vascular, inflammatory, malignancy
Symptoms, signs

- Prodromal symptoms (+/- rash)
- Fever
- Headache
- Altered Mental State, personality, behaviour
- Seizures
- Focal neurological abnormalities
- +/- Meningism (meningoencephalitis)
- +/- Peripheral neurology (encephalomyeloradiculopathy)
Diagnosis (1)
Cerebrospinal fluid

- Lymphocytic pleocytosis: 10-500/mm³
- Neutrophil pleocytosis
  - CMV radiculomyelitis
  - West Nile virus
- No pleocytosis (early disease)
- Protein elevation
- Normal-mild depressed glucose
Diagnosis (2)
Neuroimaging

- **CT scan**
  - Scout for problems that may preclude lumbar puncture
  - May be useful in HSV encephalitis (but ~40% non-diagnostic)

- **MRI**
  - Test of choice
  - Various sequences assist with diagnosis
    - Diffusion weighted images
    - T1 (with contrast)
    - T2 prolongation
    - FLAIR

- **PET scan**
Diagnosis (3)
Electroencephalography (EEG)

- Detect CNS dysfunction

- Temporal lobe localisation with slow waves, spikes, spike waves associated with HSV encephalitis
  - 80% biopsy proven HSV will have focal abnormalities EEG

- Low Specificity for HSE in some geographic contexts
  - Similar patterns with Eastern Equine Encephalitis
  - Californian Encephalitis

- Severe depression of background wave activity - poor prognostic sign
PCRPCR

- Pretest probability (clinical, imaging)
- Timing
- Quality of specimen
- Viral identification=productive infection?
Serological tests
- Serum
- CSF

Important to document baseline serology in donors/recipient to assess risk primary/reactivated disease post transplant

May be useful in documenting acute infection

CSF serology for retrospective diagnosis
Human Herpesviruses

Encephalitis in the immunocompromised host
Herpes Simplex Virus

90% acute sporadic cases of encephalitis

- **Immunocompetent**
  - Temporoparietal disease
  - > 90% HSV1 (30% primary; 70% reactivation)
  - Peaks in >60yrs

- **Immunocompromised**
  - Disseminated disease (pneumonitis, hepatitis, encephalitis)
  - Skin, eye, mouth (neonates) ~20% will progress to CNS disease without therapy
  - Atypical distribution - brainstem (AIDS)
  - HSV1/HSV2 (neonates, AIDS)
  - Disease mitigated with prophylaxis
HSV Encephalitis

Neuroimaging (1)

T2W-normal brain
Inferior temporal lobe

T2W-hyperintensity
Inferior-medial temporal lobe
Restriction on Diffusion weight MRI = more sensitive than conventional sequences. Mimics infarct
HSV Encephalitis

PCR

In brain biopsy proven HSV

- PCR Sensitivity 98%
- PCR Specificity 94%

Lakeman FD et al J Infect Dis 1995;171:857
## HSV- CSF PCR

<table>
<thead>
<tr>
<th>Days antiviral therapy</th>
<th>PCR +ve</th>
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<tr>
<td>0-7</td>
<td>100%</td>
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<tr>
<td>8-14</td>
<td>47%</td>
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<tr>
<td>&gt;15</td>
<td>21%</td>
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Lakeman FD *J Infect Dis* 1995; 171:857
Limitations HSV CSF PCR

- False positive
  - Cross contamination
  - Nested PCR

- False negative
  - Early disease (<72 hrs) *Weil A et al Clin Infect Dis 2002;34:1154*
  - Days antiviral therapy *Lakeman FD J Infect Dis 1995; 171:857*
  - Inhibitors (eg Haem)
  - Less sensitive test
HSV Encephalitis
Serology

- Positive >2 weeks after onset
  - Retrospective diagnosis

- Serum Ab: CSF Ab ($\leq 20$)

- Serum: CSF albumin (control)
HSV Encephalitis
Diagnostic issues in immunocompromised

- Prophylactic, Preemptive, Empiric antiviral use common

- Lumbar punctures often risky esp
  - Thrombocytopenia (<50,000)
    - Increased risk of bloody taps
  - Haem contamination CSF
  - Technical difficulties

** Bloody taps and antiviral may decrease sensitivity of PCR in this setting

- Volume required for a single test small but often a battery of investigations requested

- Dual pathologies not uncommon
Varicella Zoster Virus (VZV) encephalitis (1)

- **Immunocompetent**
  
  Kleinschmidt Bk et al Arch Path Lab Med 2001; 127:770

- Acute meningoencephalitis
- Reyes syndrome
- Acute Disseminated Encephalomyelitis (ADEM)
- Large vessel (granulomatous vasculitis)
Varicella Zoster Virus (VZV) encephalitis (2)

- **Immunocompromised**  
  Kleinschmidt Bk et al Arch Path Lab Med 2001; 127:770

  - **Clinical:** Herpes Zoster (+/-) followed by confusion, ataxia, fever, seizures, focal neuro deficits

  - **Pathology:**
    - Ventriculitis (Ependymal cells)
    - Multifocal leukoencephalopathy (Small vessel vasculopathy + oligodendrocyte invasion)
    - Meningoencephalitis (Meningeal Cells)
VZV encephalitis
Small vessel vasculopathy

- Cortical infarction, white matter lesions and lesions at junction of grey-white matter on MRI
  = Multifocal leukoencephalopathy
- Less coalescent than lesions seen in PML

Gilden DH et al, NEJM, 2000;342:635-646
**VZV encephalitis**

**Diagnosis**

- **VZV PCR**
  - Sensitivity and specificity >95%
  - Can be seen in CSF in uncomplicated Zoster-less specific if LP performed Close to time of Shingles eruption (dorsal root ganglia proximity to subarachnoid space)
  - Useful for monitoring response, guiding length of therapy in HIV

  *Gilden DH et al J Neurol Sci 1998; 159: 140*

- **VZV antibodies CSF**
  - Vasculopathy may result in extravasation VZV antibodies into the CSF (circumstantial evidence to support diagnosis)
40+ yr old male
Diagnosis: AML -Dx 2005, **relapsed** 2006, Cx Pulm aspergillus
Transplant: **Unrelated peripheral cell** Tx 2007 (Cy/TBI/ATG)
**Serology**
- CMV Neg (Donor Neg)
- HSV IgG+
- EBV IgG +
- VZV IgG +
- HHV6 IgG+
- HIV /HepB/Hep C Neg
Clinical vignette (1)

Clinical course

Day +12  Acute GVHD (skin, grade 2)- steroids
Day +16  Neutropenic sepsis, ICU
Day+21  Neutrophil engraftment
Day >28  Platelet transfusion dependent
Day +70  High fevers, diplopia, drowsy
          HRCT chest patchy ground glass change
          CT brain (non-contrast):NAD
          CSF Glucose normal, protein 1.22
          monos 29, neut 4 red cells 19
          Cytology atypical mononuclear cells
          MRB ? T2 intensity posterior pons
          Neck mass- right cervical adenopathy (failed
          biopsy)
Clinical vignette (1)

- Bone Marrow - hypocellular, no malignant cells seen
- CSF - no bacterial growth, crypto Ag negative, flow cyto
- PCR negative
  - CMV
  - HSV
  - VZV
  - Adenovirus
  - Enterovirus
  - HHV6
  - Toxoplasmosis
  - M.TB
- PCR positive
  - EBV

DECEASED Day+87
EBV CNS Pathology

- **Immunocompetent**
  - Mononucleosis, with CNS disease (1-5%)
  - Isolated EBV meningoencephalitis
  - Post-infectious (ADEM)

- **Immunocompromised**
  - Meningoencephalitis
  - Primary CNS Lymphoma, NHL (AIDS)
  - Post transplant Lymphoproliferative disorder (PTLD) with CNS involvement
EBV encephalopathy
Pathogenesis

- Direct CNS Infection?
  - MRI /pathology support postinfectious syndrome

- Endothelial Ab-Ag complexes
  - Demyelination (ADEM)

- Infiltration CD8+ cytotoxic cells

- Indirect:
  - CNS lymphoma in AIDs
  - PTLD- clonal expansion EBV infected B cells in presence of depleted cytotoxic T cells
EBV CNS disease
Immunocompromised

- **AIDs**
  - 20% all CNS lymphomas are primary - majority EBV related
  - Other lymphomas with potential secondary CNS involvement also EBV related (NHL, Hodgkins, Burkitts)
  - CD4<50/mm$^3$
  - EBV DNA +ve CSF high predictive lymphoma
  - EBV DNA may precede onset overt disease

- **Transplants**
  - 95% PTLD EBV associated (10% CNS disease, HSCT>SOT)
  - Decreased EBV CTL
  - Monomorphich (clonal B cell) - Tx with chemotherapy/immunotherapy
  - Polymorphic - decrease immunosuppression
  - High association D+/R-
**Cytomegalovirus encephalitis**

- Rare in immunocompetent

- In immunocompromised - mitigated with use of primary and secondary prophylaxis (transplants, HIV) and HAART in HIV

- Risk in AIDS when CD4 counts <100/mm³

- In transplantation
  - Observed as late complication HSCT
  - Predictors include prior CMV reactivations, steroids, low CD4 counts
    - **often associated with other end-organ disease (enteritis, hepatitis, pneumonitis, retinitis)**
CMV encephalitis
Diagnosis

- Culture
- Brain Biopsy
- Neuroimaging
- PCR >80% sensitivity >90% specificity
- Q PCR serum, CSF- diagnosis and monitoring response to therapy
- CMV retinitis in AIDs ~42% associated with CMV encephalitis post mortem series, 75% if retinitis peripapillary

Bylsma SS et al Arch ophthalmol 1995;113:89
CMV encephalitis
Pathology

- Isolated cytomegalic cells
- Microglial nodules- occ CMV inclusions (assoc Dementia)
- Ventriculoencephalitis
  - Destruction ependymal lining with high proportion CMV infected cells
  - Necrosis periventricular parenchyma
  - HIV patients CD4<100/mm³

CMV encephalitis

**Adult-ventriculoencephalitis**

- TW1-coronal ventriculomegaly & ependymal enhancement with gadolinium
- TW2- axial Ventriculomegaly Ependymal enhancement

**Congenital CMV**

- Non-contrast axial CT scan Ventricolomegaly & Periventricular calcification
Human Herpesvirus 6 Encephalitis

- Neurotropic and T lymphotrophic
  - Astrocytes? may be latent reservoir
  - Immunomodulatory

- Immunocompetent
  - HHV6 associate with 31% febrile convulsions in <2 yr olds
  - Case Reports of encephalitis in children and adults
    (diagnosis on PCR, immunohistochemistry brain tissue)

- Immunocompromised
  - HSCT limbic encephalitis (somnolence, short term memory loss)
    - Case reports immunstain+brain tissue + CSF PCR
    - Q PCR correlates with disease Ogata M JID 2006; 193; 68
  - Case reports SOT (esp liver, cardiac)
  - AIDs associations less clear- demyelination autopsy specimens
Human Herpesvirus 7 Encephalitis

- CD4 lymphotropic

- Viraemia in post transplant setting
  - HSCT 57%  Wang FZ Blood 1996; 88:3615
  - ? Cofactor in CMV pathogenesis

  - +ve PCR HHV7 in CSF
  - +ve HHV7 from brain stem tissue (HSV1/2, VZV, CMV, EBV, HHV6, HHV8 all negative)
  - Prior CSFs (for chemo) negative
Human Herpesvirus 8 Encephalitis

- Detected in brain biopsies HIV, dorsal root ganglia of Kaposi’s patients and in brain tissue of immunocompetent hosts.

- Associations with Castleman’s syndrome and effusion-related lymphomas, lymphoma without effusions (Brain, GIT).

- Small vessel vasculopathy/encephalitis in cases (2 HIV, one immunocompetent). Said J AIDS 1997;11:1119
Non Herpesviruses

Encephalitis in the immunocompromised host
Clinical vignette (2)

- 47 yr old female
- Lymphoma 1995, relapsed x2
- Sibling peripheral blood stem cell Tx 1999, reduced intensity conditioning (Fludarabine, cyclophosphamide)
- cGVHD- steroids, cyclosporin

Serology
CMV D+/R+
HSV +
EBV+
VZV+
HIV/Hep B/HepC neg
Clinical vignette (2)

- Presents in 2006
- I week left sided weakness, few days slurred speech, afebrile
  - CT head: NAD
  - CSF glucose normal, protein 2.67 g/dL, no white cells, 33 RBC
  - CSF bacterial cultures negative, crypto Ag neg
  - PCR Neg
    - HSV
    - VZV
    - HHV6
    - Toxo
    - M.TB
    - JC virus
- DECLINE IN NEUROLOGICAL STATUS
  - MRI
  - Brain biopsy JCV +
  - Bone Marrow Biopsy/ flow cytometry
Viral inclusions

Oligodendrocyte

White matter degeneration - Multiple foamy histiocytes

Viral inclusions oligodendrocyte
Oligodendrocyte

With ground glass nucleus
Perivascular Lymphocytic Infiltrate
JC Virus
Diagnosis

- Polyomavirus
- Rapidly progressive focal neurology
  - Ataxia, visual fields, paraesthesia, cognitive
  - Poor prognosis (death within 4-6 months of onset)
- MRI
- CSF
  - PCR JCV
- Brain Biopsy
  - Viral inclusions in oligodendrocytes
  - Immunoperoxidase +ve
  - EM+ve
JC Virus

- Asymmetric area T2 signal (white matter)

- Therapy
  - * limited data in transplant
  - Immune reconstitution (HAART) + CDV
  - IL2 (anecdotal)
  - AraC (HIV)
Enteroviruses

- Persistent fatal infections in host with hereditary, acquired defects in B lymphocytes
  - X linked agammaglobulinaemia
  - Common variable immunodeficeincy
  - HSCT
- Heightened risk of Vaccine associated paralytic polio
- Chronic hepatitis, dermatomyositis, papilloedema, encephalitis +/-meningism
- Lethargy, seizures, tremor ataxia
- Recurrent isolation enterovirus from CSF
Zoonotic Encephalitis from transplantation and transfusion  
Keeping an open mind…

- **West Nile Virus** *(MMWR Sept 2002)*
  - 2002: WNV in Transplants from infected donor or infected blood products

- **Rabies** *(MMWR July 2004)*
  - 2004: 3 deaths (liver, 2 kidneys)
  - All fatal
  - Infected donor, unrecognised exposure

- **Lymphocytic choriomeningitis** *(MMWR May 2005)*
  - 2005: 4 transplants, 3 deaths
  - Hepatitis failure
Diagnosis

- Neuroimaging (CT, MRI, PET)
- Electro encephalography (EEG)
- CSF
- PCR
- QPCR
- Multiplex PCR (herpesviruses, EV-HSV, polyomaviruses)
- Serology (serum:CSF)
- Brain Biopsy